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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,342	09/18/2000	Rudi Brands	01975.0025	8325
22852 7590 08/24/2007 FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP 901 NEW YORK AVENUE, NW WASHINGTON, DC 20001-4413			EXAMINER FORD, ALLISON M	
			ART UNIT 1651	PAPER NUMBER
			MAIL DATE 08/24/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/582,342

Applicant(s)

BRANDS, RUDI

Examiner

Allison M. Ford

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 November 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,7,8,11-18,23-25 and 27-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,7,8,11-18,23-25 and 27-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on 23 June 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application
- ☐ Other: _____.

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DETAILED ACTION

Applicant's reply of 9 December 2006 has been received and entered into the application file. Claims 1 and 27 have been amended; new claims 28-38 have been added; claims 1, 2, 7, 8, 11-18, 23-25 and 27-38 are pending in the current application, all of which have been considered on the merits.

Please note, this application has been transferred to examiner Allison Ford of Art Unit 1651, whose contact information can be found at the conclusion of this Office Action.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 371, which papers have been placed of record in the file. Additionally, acknowledgment is made of applicant's claim for foreign priority based on PCT/EP98/08522 filed on 17 December 1998, which further claims priority to Dutch application 97204110.7 filed on 24 December 1997. A certified copy of the foreign priority application is present in the instant application file.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 7, 8, 11-18, 23-25 and 27-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, steps (c), (d) and (f) are indefinite as failing to particularly point out and claim what positive action is to be performed. For example, steps (c) and (f) recite "*employing* said first part (a first portion) ...*for the preparation* of at least one subsequent..." Step (d) recites

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“employing said second part as a seed for the preparation of at least one subsequent...” It is not clear in these steps what is actually being done, rather only that the cell populations are being used for ‘preparation’ of something else. It would be remedial to simplify the language to recite a single positive step..

Also, in claim 1, steps (e) and (g) are disclosed as “optional” this renders the claim indefinite because it is not clear if these steps are required as part of the claimed method or not, thus the metes and bounds of the claims are not clear.

Still further, in claim 1, an essential step appears to have been omitted, said omission amounting to a gap between the steps, the omitted step being: a step of dividing the expanded subsequent preproduction batch into a first and second portion. This step should appear after step (e) and prior to step (f).

Still further, step (g) is unclear in as far as it recites “wherein the repeating comprises obtaining a second portion of the cells of the subsequent preproduction batch of d) or e)....” It appears that Applicants are intending for steps (b)-(e) to be repeated, it is not clear what steps f) and g) add to the method beyond repetition of already claimed steps. Amending the claim to require repetition of only steps (b)-(e) (see below) would appear to be remedial.

Still further, it is noted that requiring the cells of the production batch of (c) to have a different passage number than cells of subsequent production batches (such as in step (f)) does not further limit the claimed method, but rather discloses an inherent property (due to the required steps, when the initial production batch of step (c) has a passage number of X, the subsequent production batches would have to have a passage number of at least X+1). While it is permissible to recite an inherent property in the claim language, in the instant case this confuses the claim.

The following language is suggested to correct for the above described causes of indefiniteness:

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“A method for producing at least one virus from MDCK cells, said method comprising:

- (a) culturing MDCK cells on a substrate to form a preproduction batch;
- (b) dividing said cells of the preproduction batch into a first production batch comprising approximately 80%-90% of the cells, and a second seed batch comprising approximately 10%-20% of the cells;
- (c) culturing the cells of the first production batch to produce at least one virus;
- (d) culturing the cells of the second seed batch to form at least one subsequent preproduction batch; and

(e) repeating steps (b)-(d) with the subsequent preproduction batch of (d);

wherein the passage number of the cells of each production batch is between master cell bank and extended cell bank.”

Additionally, for purposes of clarity, claim 2 would be clearer if written, “The method of claim 1, wherein step (b) dividing said cells of the preproduction batch involves transferring each of the first and second parts (into/onto new/separate/different culture vessels).” Wherein the parenthetical portion is not required, but may aid in clarifying the step.

In claim 27, step (b) it is not clear how the at least one first production batch and at least one second production batch are ‘formed’. The step of ‘forming’ is unclear, as it necessarily requires an action greater than dividing the original preproduction batch, as the claim requires the first production batch and second production batch to have different passage numbers. It is not clear if an essential step is being omitted, said omitted step being passaging either the first or second production batch at least one additional time compared to the other production batch.

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Claim 28 is rejected as lacking antecedent basis for the limitation "the at least one subsequent preproduction batch." Claim 27 does not recite any subsequent preproduction batches.

Claim 34 and 36 and dependents thereof are rejected as lacking proper antecedent basis for the limitation "the cells" it is not clear which cells the claims are referring to (cells of preproduction batch, cells of first production batch or cells of second production batch).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Applicants' arguments against the rejection previously of record have been fully considered, but are moot in view of the new grounds of rejection.

Claims 1, 2, 7, 8, 11-18, 23-25 and 27-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (Scale-up of Suspension and Anchorage-Dependent Animal Cells in Basic Cell Culture Protocols, Edited by Pollard et al. Humana Press Inc., 1997, pp.59-75), and Pollard (Basic Cell Culture Protocols, Edited by Pollard et al. Humana Press Inc., 1997, Step 14-20 on page 3 and Section 3.2 on page 4-5). The discussion of the history of "Amish Friendship Bread" pulled from <http://recipecircus.com> ("Friendship Cake/Bread History") and <http://en.wikipedia.org> ("Amish Friendship Bread") are also relied upon in this rejection to establish the definition and recipe of the bread recipe which calls for a starter culture.

The methods as currently claimed require the culture of MDCK cells on a substrate, splitting of the culture, wherein one portion/part of the culture is utilized for production of viruses, and the other portion/part of the culture is passaged and used to repeat the cycle. The

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claims also require that the cells which are used for production of viruses have a passage number between "master cell bank" (MCB) and "extended cell bank" (ECB); from the specification these terms are understood to define the passage numbers during which the cells can successfully produce the desired biological product, thus between the time the cells are considered MCB and ECB, the cells are useful for producing the desired biological. Additionally some claims require that the passage number of cells split and used for production of viruses to be different during each cycle, (e.g. cells of first split to have a passage number of X, cells from next split to have a passage number of X+1, etc); however, this is an inherent property of the cells when the method as claimed is carried out. Dependent claims further define various culture, splitting, and production conditions. The method is found to be obvious in view of the knowledge available to one of ordinary skill in the art, at the time the invention was made, and thus does not represent a novel or non-obvious contribution over the art.

MDCK cells are notoriously old and well known in the art for their use in culture to grow viruses (dating back to at least the 70s). Therefore it would have been obvious at the time the invention was made to split and passage MDCK cells, and use for the production of viruses. Methods of splitting and passaging MDCK cells, as well as methods of using cultures of MDCK cells for production of viruses or other biologicals, are disclosed by Griffiths et al and Pollard, the details of which have been made of record previously.

It is noted that while Griffith et al and Pollard disclose means to split cultures of adherent MDCK cells, they do not explicitly state that the original culture is split in at least two portions/parts, wherein at least a first portion/part is used for production of viruses, and at least a second portion/part is retained, replated and expanded (passaged), in order to maintain the cell line and be further split for the process to be repeated. However, passage of the at least a second portion/part is an obvious step that would be routinely performed by the skilled artisan. By retaining and passaging at least one portion/part of the culture one is able to continue the cell line,

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thereby saving money (by not needing to purchase a subsequent cell culture seed), and increasing the amount of virus (biological product) which can ultimately be produced (as the initial culture is not exhausted after the first round of virus production, but a small portion can be retained, passaged and expanded, so as to replenish the production batch).

With regards to limitation regarding the cells being used for production of viruses having a passage number between MCB and ECB, it is submitted that because this range merely defines the time period (by passage number) during which the cells would be reasonably be expected to successfully produce viruses, selection of the cells which would fall within this time period would be a matter of routine optimization, as well as quality control (so as to ensure the desired product is being produced), which would be well within the purview of the skilled artisan.

The concept of splitting a culture, using the majority of it for production of a biological product, and retaining the subsequent portion for passage and expansion is a common method, for example in production of sourdough or "Friendship Bread" (See, for example, "Friendship Cake/Bread History" from <http://recipecircus.com> (accessed 8/6/2007); or the discussion at Wikipedia under "Amish Friendship Bread" (accessed 8/6/2007)) which involves dividing of a starter culture into two portions, using one portion for the production of the bread, and sharing the other portion with a friend, wherein the friend can repeat the process; in such a manner single cultures can exist for years.

Therefore, the instantly claimed method is not considered to be patentably, as it is obvious to one of ordinary skill, as one would know how to culture MDCK cells to produce a virus, and it would be common sense to maintain a portion of the cell culture during each split, to replenish the original culture and use to repeat the process, thereby prolonging the culture life and increasing the amount of culture which can be used to produce the desired virus product. It is further pointed out that support for this rationale, that common sense must be taken into account, and may be rationale for rendering an invention patentable, was verified in the recent Supreme

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Court decision of *KSR International Co vs. Teleflex Inc.* Specifically, the Supreme Court held that "Variations of particular work available in one field of endeavor may be prompted by design incentives and other market forces, either in same field or different one, and if person of ordinary skill in art can implement predictable variation, 35 U.S.C. §103 likely bars its patentability; similarly, if particular technique has been used to improve one device, and person of ordinary skill would recognize that it would improve similar devices in same way, then using that technique is obvious unless its actual application is beyond person's skill, and court resolving obviousness issue therefore must ask whether improvement is more than predictable use of prior art elements according to their established functions." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1386. Serial passaging of an MDCK cell culture, for the continued production of viruses, a biological product, is not considered outside the skill of one of ordinary skill in the art, particularly in view of the fact that such serial passaging means were routinely known (see, e.g., sourdough/ "Amish Friendship Bread" recipes) and used for the purposes of prolonging cultures for production of a biological product, whether the product be bread or viruses useful for other research or vaccine purposes, the outcome and resourcefulness is the same. Therefore, the logic behind the instant invention is no more than common sense which had routinely been exhibited in the art, prior to the instant invention.

Finally, with regards to the variations and limitations of the various dependent claims, it has previously been submitted that such limitations are merely results of routine optimization, which would have been obvious to one of ordinary skill in the art at the time the invention was made. Specifically, it has been held that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which

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differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

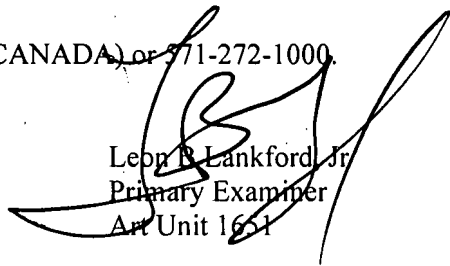
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Leon B. Lankford, Jr.
Primary Examiner
Art Unit 1651